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Original research paper

Green ultrasound-assisted three-component click synthesis of novel 1*H*-1,2,3-triazole carrying benzothiazoles and fluorinated--1,2,4-triazole conjugates and their antimicrobial evaluation

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The present study describes an efficient and ecofriendly, ultrasound, one- pot click cycloaddition approach for the construction of a novel series of 1,4-disubstituted-1,2,3-triazoles tethered with fluorinated 1,2,4-triazole-benzothiazole molecular conjugates. It involved three- component condensation of the appropriate bromoacetamide benzothiazole, sodium azide and 4-alkyl/aryl-5-(2-fluorophenyl)-3-(prop-2-ynylthio)-1,2,4-triazoles **4a-e** through a Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction. This approach involves *in situ* generation of azidoacetamide benzothiazole, followed by condensation with terminal alkynes in the presence of $CuSO_4$/Na-ascorbate in aqueous DMSO under both conventional and ultrasound conditions. Some of the designed 1,2,3-triazole conjugates **6a-o** were recognized for their antimicrobial activity against some bacterial and fungal pathogenic strains.

Keywords: benzothiazoles, 1,2,3-triazoles, 1,2,4-triazoles, click synthesis, antimicrobial

Benzothiazole heterocycles constitute an important class of nitrogen-containing heterocycles associated with a wide array of biological and pharmaceutical activities (1, 2). Similarly, 1,2,4-triazoles are the most significant scaffolds in many drug structures, including fluconazole (3), isavuconazole (4), itraconazole (5) and voriconazole (6) as antifungal agents. In addition, 1,2,3-triazoles have emerged as relevant bioactive azoles with promising medicinal potentials, including anti-inflammatory (7), antitubercular (8), antiproliferative (9), anticancer (10, 11) antimicrobial and cytotoxic (12).

Synthesis of regioisomeric 1,4-disubstituted 1,2,3-triazoles through copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of terminal alkynes with organoazides is one of the most popular examples of the so-called click chemistry in modern heterocycle synthesis (13). In addition, the copper catalyzed one-pot multicomponent regioselective preparation of 1,2,3-triazoles has attracted a great deal of interest owing to its many advantages,

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including simple experimental procedures or mild reaction conditions, reduction of waste, energy efficiency, reduced reaction time and minimized risk of handling hazardous azides, along with the introduction of eco-friendly sonochemistry for rapid synthesis (14, 15).

Ultrasound methods have gained a great deal of interest as alternative sources of energy and have an outstanding status in organic synthesis. Most of the research concerning the application of ultrasound (US) in organic synthesis has been characterized by significant reduction in reaction time and improvement of product yields (16). The obvious advantage of this technique is that its application in organic reactions makes this tool more effective and ecofriendly (17).

In our early work, we investigated the synthesis and antimicrobial screening of new 1,2,3-triazoles bonded to a benzothiazole ring *via* an acetamide spacer by both conventional and ultrasound procedures (18). As a continuation of our efforts to design conjugates with therapeutic potential (19, 20), the present manuscript utilizes one-pot synthesis and antimicrobial evaluation of novel 1,2,3-triazoles tethered to benzothiazole and 5-(2-fluorophenyl)-1,2,4-triazole conjugates with well-modulated thiomethylene and/or acetamide spacers. Target scaffolds were synthesized by combining click chemistry (azide-alkyne cycloaddition) and MCR (multicomponent reaction) approaches. Recently, MCR strategy has been extensively adopted in modern heterocyclic chemistry for the construction of a broad array of heterocyclic scaffolds, including imidazoles (21), thiazolidi-4-ones (22), dihydropyrimidin-ones/thiones (23), *etc*.

EXPERIMENTAL

Melting points were measured on a melt-temp apparatus (SMP10) (Stuart, UK) and are uncorrected. The IR spectra were measured using a Perkin-Elmer 1430 series FT-IR spectrometer (Perkin-Elmer, USA) as potassium bromide pellets. ^{1}H NMR spectra were recorded using an Advance Bruker NMR spectrometer (Bruker, Switzerland) at 400–600 MHz, while ^{13}C NMR spectra were recorded on the same instrument at 100–150 MHz using tetramethylsilane (TMS) (δ, ppm) as the internal standard. The EI mass spectra were measured with a Finnigan MAT 95XL spectrometer (Finnigan, Germany). Sonochemical reactions were performed in a Kunshan KQ-250B ultrasound cleaner (50 kHz, 240 W, China).

General synthesis procedures

Two methods for propargylation of 4-alkyl/aryl-5-(2-fluorophenyl)-2,4-dihydro-1,2,4-triazole-3-thiones **3a**-**e** to 4-alkyl/aryl-5-(2-fluorophenyl)-3-(prop-2-ynylthio)-1,2,4-triazoles **4a**-**e** were used.

Conventional method (CM). – A stirred mixture of the appropriate triazole **3a-e (**10 mmol), triethylamine (10 mmol) and propargyl bromide (10 mmol) in absolute ethanol (50 mL) was refluxed for 1–2 h. Excess ethanol was removed under vacuum and the resulting product was recrystallized from ethanol to yield the desired propargylated triazole **4a-e**.

Ultrasound method (US). – A mixture of the appropriate triazole **3a-e (**1 mmol), triethylamine (1 mmol), propargyl bromide (1 mmol) and absolute ethanol (5 mL) was irradi-

ated by ultrasound for 15–20 min at room temperature in a laboratory ultrasonic cleaning bath. The reaction mixture was processed as described above to afford the same products **4a-e**.

Procedures for the synthesis of click products *N*-(un/substituted benzo[*d*]thiazol-2-yl)-4-alkyl/aryl-2-(4-(((5-(2-fluorophenyl)-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)-acetamides **6a**-**o** are given below.

Conventional method (CM). – To a stirring solution of the appropriate α-bromoacetamide benzothiazole **5a-c** (1 mmol) dissolved in a mixture of DMSO and water (1:1), sodium azide (1.5 mmol) was added. Then, the appropriate propargylated triazole **4a-e** (1 mmol), $CuSO_4$ (0.01 mmol), and Na-ascorbate (0.02 mol) were added under stirring at 100 °C for 36–48 h. After completion of the reaction (reaction was monitored by TLC), the reaction mixture was quenched with a saturated solution of sodium chloride (brine solution). The aqueous layer was then extracted with ethyl acetate (3 × 20 mL). Removal of the solvent under reduced pressure furnished the targeted click products **6a-o,** which were crystallized from ethanol/DMF.

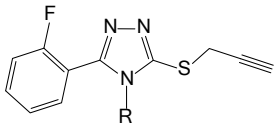
Ultrasound method (US). – A mixture of the appropriate α-bromoacetamide benzothiazole **5a-c** (1 mmol), sodium azide (1.5 mmol), the appropriate propargylated triazole **4a-e** (1 mmol), $CuSO_4$ (0.01 mmol) and Na-ascorbate (0.02 mol) in DMSO/H_2O (1:1) was irradiated under ultrasound for 6–8 min at room temperature in a laboratory ultrasonic cleaning bath. The reaction mixture was processed as described above to afford the same click products **6a-o**.

Physicochemical and spectral data (MS, IR, ^{1}H- and ^{13}C NMR) for the newly synthesized products **4a-e** and **6a-o** are collected in Tables I and II.

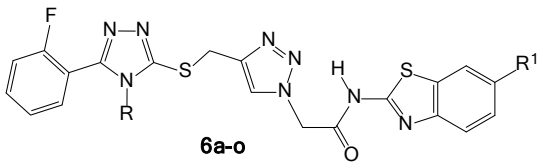
Antimicrobial susceptibility testing

Clinical isolates tested in this study were obtained from the culture collection maintained at the RCMB (Regional Center for Mycology and Biotechnology/Antimicrobial Unit test organisms, Al Azhar University, Cairo, Egypt). The newly designed compounds were evaluated for their antimicrobial activity against six pathogenic bacterial strains [Gram-positive: *Bacillus subtilis* (RCMB 010067), *Streptococcus pneumoniae* (RCMB 010010) and *Staphylococcus aureus* (RCMB 010025), Gram-negative: *Escherichia coli* (RCMB 010052), *Pseudomonas aeruginosa* (RCMB 010043) and *Klebsiella pneumoniae* (RCMB 010058), and two fungal strains (*Aspergillus fumigatus* (RCMB 02568) and *Candida albicans* (RCMB 05036)] by the broth microdilution method (24, 25). Tested compounds (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL) and then diluted in culture medium (Müller-Hinton broth for bacteria and Sabouraud liquid medium for fungi) with further progressive dilutions to obtain final concentrations of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250 and 500 mg mL^{-1}. The DMSO content never exceeded 1 %, *V*/*V*. The tubes were inoculated with 105 cfu mL^{-1} (colony forming units mL^{-1}) and incubated at 37 °C for 24 h. Growth controls consisting of media and media with DMSO in the same dilutions as used in the experiments were employed. Antimicrobial activities were expressed in terms of the minimum inhibitory concentration (*MIC*) and are presented in Table III. Each experiment was carried out in triplicate and the average *MIC* was calculated.

*Table I. Physicochemical data for the newly synthesized compounds **4a-e** and **6a-o***



4a-e



6a-o

Compd.	R	R^1	M. p. (°C)	Conventional method		Ultrasound method	
				Time (h)	Yield (%)	Time (min)	Yield (%)
4a	CH_3	–	90–91	1	93	15	98
4b	CH_2CH_3	–	99–100	1	92	15	97
4c	$CH_2CH{=}CH_2$	–	119–120	1.5	90	20	94
4d	CH_2Ph	–	105–106	1	92	15	97
4e	Ph	–	131–132	2	91	20	95
6a	CH_3	H	180–181	36	86	6	94
6b	CH_3	CH_3	140–141	36	84	6	94
6c	CH_3	SO_2CH_3	235–236	40	82	7	91
6d	CH_2CH_3	H	163–164	38	85	6	93
6e	CH_2CH_3	CH_3	129–130	40	83	7	90
6f	CH_2CH_3	SO_2CH_3	212–213	44	82	7	89
6g	$CH_2CH{=}CH_2$	H	198–199	40	81	7	87
6h	$CH_2CH{=}CH_2$	CH_3	156–157	44	80	7	86
6i	$CH_2CH{=}CH_2$	SO_2CH_3	264–265	48	79	8	85
6j	CH_2Ph	H	150–151	38	84	6	92
6k	CH_2Ph	CH_3	123–124	38	82	7	91
6l	CH_2Ph	SO_2CH_3	173–174	40	81	7	89
6m	Ph	H	191–192	40	82	7	89
6n	Ph	CH_3	163–164	44	81	7	87
6o	Ph	SO_2CH_3	255–256	48	80	8	86

*Table II. IR, ^{1}H- and ^{13}C NMR spectral data for the newly synthesized compounds **4a-e** and **6a-o***

Compd.	Theor. M exp. MS: [M+]	Calcd./found (%) C	H	N	IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
4a	247.06 247	58.28 58.12	4.08 4.19	16.99 17.11	1563 (C=C), 1645 (C=N), 2110 (C≡C), 2950 (C-H al), 3074 (C-H ar), 3320 (≡CH)	2.26 (s, 1H, ≡CH), 3.51 (s, 3H, CH_3), 3.90 (s, 2H, SCH_2), 7.13-7.24 (m, 2H, Ar-H), 7.47-7.57 (m, 2H, Ar-H)	2.48 (SCH_2), 31.45 (CH_3), 72.80 (≡CH), 78.31 (C≡C), 115.06, 115.20, 115.95, 116.16, 124.92, 124.95, 132.11, 132.70, 132.78, 150.22, 152.44, 158.46, 160.94 (Ar-C, C=N)
4b	261.07 261	59.75 59.88	4.63 4.56	16.08 16.23	1555 (C=C), 1670 (C=N), 2120 (C≡C), 2970 (C-H al), 3090 (C-H ar), 3340 (≡CH)	1.50 (t, 3H, CH_3), 2.24 (s, 1H, ≡CH), 3.87 (s, 2H, SCH_2), 3.84-3.90 (q, 2H, NCH_2), 7.15-7.26 (m, 2H, Ar-H), 7.50-7.56 (m, 2H, Ar-H)	15.78 (CH_3), 22.89 (SCH_2), 37.56 (NCH_2), 73.15 (≡CH), 77.82 (C≡C), 114.88, 115.14, 116.12, 116.67, 124.67, 125.45, 131.31, 132.14, 132.82, 150.45, 152.57, 158.65, 160.87 (Ar-C, C=N)
4c	273.07 273	61.52 61.64	4.43 4.38	15.37 15.49	1578 (C=C), 1628 (C=N), 2115 (C≡C), 2918 (C-H al), 3024 (C-H ar) 3300 (≡CH)	2.29 (s, 1H, ≡CH), 4.01 (s, 2H, SCH_2), 4.64 (d, 2H, J = 4 Hz, NCH_2), 5.02 (dd, 1H, J = 4, 12 Hz, =CH), 5.36 (dd, 1H, J = 4, 12 Hz, =CH), 5.91-5.96 (m, 1H, SCH_2CH), 7.19-7.29 (m, 2H, Ar-H), 7.54-7.62 (m, 2H, Ar-H)	22.39 (SCH_2), 46.87 (NCH_2), 72.69 (≡CH), 78.30 (C≡C), 115.54, 115.77, 117.24, 117.45, 118.48, 124.15, 124.18, 128.80, 128.89, 130.65, 130.75, 131.30, 150.68, 152.99, 158.48, 160.94 (Ar-C, C=N)
4d	323.09 323	66.85 66.68	4.36 4.49	12.99 12.84	1590 (C=C), 1650 (C=N), 2130 (C≡C), 2965 (C- H al), 3040 (C-H ar), 3350 (≡CH)	2.28 (s, 1H, ≡CH), 3.89 (s, 2H, NCH_2), 4.08 (s, 2H, SCH_2), 6.94-7.00 (m, 1H, Ar-H), 7.18-7.29 (m, 3H, Ar-H), 7.41-7.52 (m, 5H, Ar-H)	22.37 (SCH_2), 39.97 (NCH_2), 73.66 (≡CH), 78.38 (C≡C), 115.69, 115.92, 117.17, 117.38, 124.20, 124.23, 129.18, 129.27, 130.71, 130.80, 135.98, 151.59, 152.62, 158.51, 160.90 (Ar-C, C=N)
4e	309.07 309	66.00 66.12	3.91 4.07	13.58 13.70	1550 (C=C), 1635 (C=N), 2110 (C≡C), 2955 (C- H al), 3075 (C-H ar), 3350 (≡CH)	2.28 (s, 1H, ≡CH), 4.08 (s, 2H, SCH_2), 6.94-6.98 (m, 1H, Ar-H), 7.18-7.28 (m, 3H, Ar-H), 7.42-7.46 (m, 4H, Ar-H), 7.59-7.62 (m, 1H, Ar-H)	21.18 (SCH_2), 72.46 (≡CH), 78.15 (C≡C), 115.13, 115.28, 115.84, 116.05, 124.47, 124.51, 126.48, 126.49, 126.54, 129.49, 129.54, 129.67, 131.88, 131.90, 132.34, 132.42, 135.52, 151.28, 151.84, 158.36, 160.86 (Ar-C, C=N)

6a	480.09	52.49	3.57	23.32	1580 (C=C), 1645 (C=N), 1690 (C=O), 2950 (C-H al), 3050 (C-H ar), 3380 (N-H)	3.37 (s, 3H, CH_3), 4.52 (s, 2H, SCH_2), 5.53 (s, 2H, NCH_2CO), 7.32-7.39 (m, 2H, Ar-H), 7.42-7.47 (m, 2H, Ar-H), 7.61-7.64 (m, 2H, Ar-H), 7.79 (d, 1H, *J* = 4 Hz, Ar-H), 7.99 (d, 1H, *J* = 4 Hz, Ar-H), 8.08 (s, 1H, CH-1,2,3-triazole), 12.87 (s, 1H, NH)	28.01 (SCH_2), 31.15 (CH_3), 51.68 (NCH_2CO), 115.03, 115.10, 116.23, 116.32, 121.86, 123.90, 125.12, 125.14, 125.44, 131.97, 132.97, 133.00, 142.80, 150.35, 151.29, 158.79, 159.95 (Ar-C, C=N, C=O)
	480	52.68	3.48	23.52			
6b	494.11	53.43	3.87	22.66	1630 (C=N), 1680 (C=O), 2925 (C-H al), 3030 (C-H ar), 3340 (N-H).	2.41 (s, 3H, CH_3), 3.37 (s, 3H, NCH_3), 4.53 (s, 2H, SCH_2), 5.51 (s, 2H, NCH_2CO), 7.27 (d, 1H, *J* = 4 Hz, Ar-H), 7.38-7.44 (m, 2H, Ar-H), 7.61-7.67 (m, 3H, Ar-H), 7.76 (s, 1H, Ar-H), 8.08 (s, 1H, CH-1,2,3-triazole), 12.79 (s, 1H, NH)	21.02 (CH_3), 27.97 (SCH_2), 31.17 (NCH_3), 51.69 (NCH_2CO), 114.99, 115.06, 116.23, 116.33, 121.43, 125.12, 125.14, 125.47, 127.66, 131.97, 132.99, 133.03, 133.43, 142.85, 150.35, 151.45, 158.63, 159.89 (Ar-C, C=N, C=O)
	494	53.63	3.78	22.50			
6c	558.07	47.30	3.43	20.06	1565 (C=C), 1630 (C=N), 1685 (C=O), 2970 (C-H al), 3060 (C-H ar) 3340 (N-H)	3.25 (s, 3H, CH_3), 3.38 (s, 3H, NCH_3), 4.54 (s, 2H, SCH_2), 5.56 (s, 2H, NCH_2CO), 7.38-7.44 (m, 2H, Ar-H), 7.61-7.63 (m, 2H, Ar-H), 7.96-7.99 (m, 2H, Ar-H), 8.10 (s, 1H, CH-1,2,3-triazole), 8.65 (s, 1H, Ar-H), 12.83 (s, 1H, NH)	27.89 (SCH_2), 31.17 (NCH_3), 44.03 (CH_3), 51.72 (NCH_2CO), 114.98, 115.05, 116.23, 116.33, 121.11, 122.25, 124.97, 125.15, 125.50, 131.96, 132.08, 132.99, 133.02, 135.69, 142.96, 150.47, 151.39, 158.78, 159.94 (Ar-C, C=N, C=O)
	558	47.08	3.51	20.17			
6d	494.11	53.43	3.87	22.66	1510 (C=C), 1640 (C=N), 1665 (C=O), 2955 (C-H al), 3080 (C-H ar), 3320 (N-H)	1.56 (t, 3H, CH_3), 4.18-4.25 (q, 2H, NCH_2), 4.55 (s, 2H, SCH_2), 5.55 (s, 2H, NCH_2CO), 7.30-7.37 (m, 2H, Ar-H), 7.41-7.47 (m, 2H, Ar-H), 7.64-7.68 (m, 2H, Ar-H), 7.77 (d, 1H, *J* = 4 Hz, Ar-H), 7.95 (d, 1H, *J* = 4 Hz, Ar-H), 8.06 (s, 1H, CH-1,2,3-triazole), 12.80 (s, 1H, NH)	14.68 (CH_3), 27.92 (SCH_2), 41.14 (NCH_2), 51.59 (NCH_2CO), 115.13, 115.20, 116.19, 116.30, 121.78, 123.98, 125.08, 125.15, 125.49, 132.88, 133.02, 133.13, 142.85, 150.41, 151.34, 158.84, 159.89 (Ar-C, C=N, C=O)
	494	53.23	3.98	22.48			
6e	508.13	54.32	4.16	22.03	1530 (C=C), 1595 (C=N), 1640 (C=O), 2980 (C-H al), 3045 (C-H ar), 3310 (N-H)	1.54 (t, 3H, CH_3), 4.16-4.22 (q, 2H, NCH_2), 4.58 (s, 2H, SCH_2), 5.54 (s, 2H, NCH_2CO), 7.29 (d, 1H, *J* = 4 Hz, Ar-H), 7.40-7.47 (m, 2H, Ar-H), 7.65-7.70 (m, 3H, Ar-H), 7.72 (s, 1H, Ar-H), 8.10 (s, 1H, CH-1,2,3-triazole), 12.76 (s, 1H, NH)	14.66 (CH_2CH_3), 21.14 (CH_3), 27.88 (SCH_2), 41.20 (NCH_2), 51.64 (NCH_2CO), 114.87, 115.10, 116.29, 116.28, 121.51, 125.18, 125.23, 125.50, 127.72, 131.94, 132.89, 133.08, 133.39, 142.86, 150.37, 151.51, 158.82, 159.90 (Ar-C, C=N, C=O)
	508	54.11	4.28	21.90			

6f	572.08	48.24	3.70	19.57	1500 (C=C), 1625 (C=N), 1640 (C=O), 2940 (C-H al), 3045 (C-H ar), 3420 (N-H)	1.53 (t, 3H, CH_3), 4.14-4.20 (q, 2H, NCH_2), 4.57 (s, 2H, SCH_2), 5.53 (s, 2H, NCH_2CO), 7.35-7.40 (m, 2H, Ar-H), 7.63-7.68 (m, 2H, Ar-H), 7.91-7.96 (m, 2H, Ar-H), 8.12 (s, 1H, CH-1,2,3-triazole), 8.60 (s, 1H, Ar-H), 12.77 (s, 1H, NH)	14.63 ($CH_2\mathbf{C}H_3$), 27.85 (SCH_2), 41.12 (CH_3), 44.26 (NCH_2), 51.58 ($\mathbf{N}CH_2CO$), 114.92, 115.11, 116.20, 116.40, 121.15, 122.20, 124.94, 125.10, 125.53, 131.92, 132.11, 132.94, 133.05, 135.73, 143.02, 150.50, 151.42, 158.82, 159.97 (Ar-C, C=N, C=O)
	572	48.08	3.81	19.41			
6g	506.11	54.53	3.78	22.12	1570 (C=C), 1620 (C=N), 1695 (C=O), 2915 (C-H al), 3095 (C-H ar), 3375 (N-H)	4.60 (s, 2H, SCH_2), 4.87 (d, 2H, J = 4 Hz, NCH_2), 5.25 (dd, 1H, J = 4, 12 Hz, =CH), 5.52-5.58 (m, 3H, NCH_2CO, =CH), 6.10-6.15 (m, 1H, SCH_2CH), 7.30-7.36 (m, 2H, Ar-H), 7.47-7.51 (m, 2H, Ar-H), 7.65-7.69 (m, 2H, Ar-H), 8.00 (d, 1H, J = 4 Hz, Ar-H), 8.06 (s, 1H, CH-1,2,3-triazole), 12.82 (s, 1H, NH)	28.05 (SCH_2), 45.31 (NCH_2), 51.63 ($\mathbf{N}CH_2CO$), 115.09, 115.20, 116.18, 116.28, 118.59, 122.02, 123.84, 125.20, 125.26, 125.39, 128.75, 132.06, 132.88, 133.11, 142.83, 150.42, 151.27, 158.68, 159.90 (Ar-C, C=N, C=O)
	506	54.69	3.89	21.99			
6h	520.13	55.37	4.07	21.52	1575 (C=C), 1625 (C=N), 1685 (C=O), 2915 (C-H al), 3045 (C-H ar), 3335 (N- H)	2.36 (s, 3H, CH_3), 4.58 (s, 2H, SCH_2), 4.85 (d, 2H, J = 4 Hz, NCH_2), 5.20 (dd, 1H, J = 4, 12 Hz, =CH), 5.50-5.57 (m, 3H, NCH_2CO, =CH), 6.11-6.16 (m, 1H, SCH_2CH), 7.26 (d, 1H, J = 4 Hz, Ar-H), 7.37-7.45 (m, 2H, Ar-H), 7.62-7.69 (m, 3H, Ar-H), 7.74 (s, 1H, Ar-H), 8.11 (s, 1H, CH-1,2,3-triazole), 12.79 (s, 1H, NH)	21.12 (CH_3), 27.99 (SCH_2), 45.25 (NCH_2), 51.72 ($\mathbf{N}CH_2CO$), 115.01, 115.16, 116.22, 116.30, 118.62, 122.13, 125.23, 125.30, 125.53, 127.70, 128.80, 131.90, 132.92, 133.10, 133.34, 142.90, 150.31, 151.48, 158.79, 159.98 (Ar-C, C=N, C=O)
	520	55.46	4.19	21.67			
6i	584.09	49.30	3.62	19.17	1560 (C=C), 1630 (C=N), 1670 (C=O), 2895 (C-H al), 3015 (C-H ar), 3290 (N-H)	3.29 (s, 3H, CH_3), 4.55 (s, 2H, SCH_2), 4.81 (d, 2H, J = 4 Hz, NCH_2), 5.21 (dd, 1H, J = 4, 12 Hz, =CH), 5.51-5.59 (m, 3H, NCH_2CO, =CH), 6.13-6.17 (m, 1H, SCH_2CH), 7.30-7.38 (m, 2H, Ar-H), 7.66-7.71 (m, 2H, Ar-H), 7.90-7.95 (m, 2H, Ar-H), 8.08 (s, 1H, CH-1,2,3-triazole), 8.63 (s, 1H, Ar-H), 12.75 (s, 1H, NH)	27.89 (SCH_2), 43.96 (CH_3), 45.30 (NCH_2), 51.80 ($\mathbf{N}CH_2CO$), 115.05, 115.11, 116.17, 116.39, 121.20, 122.29, 125.02, 125.18, 125.56, 128.71, 128.87, 131.90, 132.08, 133.03, 133.11, 135.65, 142.91, 150.50, 151.44, 158.84, 159.90 (Ar-C, C=N, C=O)
	584	49.45	3.54	19.38			

6j	556.13	58.26	3.80	20.13	1580 (C=C), 1620 (C=N), 1715 (C=O), 2900 (C-H al), 3080 (C-H ar), 3490 (N-H)	4.50 (s, 2H, SCH_2), 4.92 (s, 2H, NCH_2), 5.61 (s, 2H, NCH_2CO), 7.17-7.25 (m, 2H, Ar-H), 7.30-7.38 (m, 3H, Ar-H), 7.45-7.54 (m, 6H, Ar-H), 7.76 (d, 1H, *J* = 4 Hz, Ar-H), 7.95 (d, 1H, *J* = 4 Hz, Ar-H), 8.11 (s, 1H, CH-1,2,3-triazole), 12.77 (s, 1H, NH)	26.58 (SCH_2), 46.52 (NCH_2), 52.34 (NCH_2CO), 113.74, 113.95, 115.89, 116.04, 121.79, 123.67, 124.74, 124.81, 126.28, 126.78, 129.46, 129.65, 132.45, 132.72, 133.08, 133.19, 139.90, 150.34, 151.56, 158.48, 159.57 (Ar-C, C=N, C=O)
	556	58.38	3.91	20.32				
6k	570.14	58.93	4.06	19.64	1590 (C=C), 1610 (C=N), 1730 (C=O), 2910 (C-H al), 3070 (C-H ar), 3480 (N- H)	2.39 (s, 3H, CH_3), 4.52 (s, 2H, SCH_2), 4.95 (s, 2H, NCH_2), 5.59 (s, 2H, NCH_2CO), 7.19-7.24 (m, 2H, Ar-H), 7.32-7.39 (m, 3H, Ar-H), 7.40-7.48 (m, 3H, Ar-H), 7.51-7.56 (m, 2H, Ar-H), 7.70 (d, 1H, *J* = 4 Hz, Ar-H), 7.81 (s, 1H, Ar-H), 8.14 (s, 1H, CH-1,2,3-triazole), 12.79 (s, 1H, NH)	21.19 (CH_3), 26.62 (SCH_2), 46.59 (NCH_2), 52.39 (NCH_2CO), 113.82, 113.98, 115.81, 116.00, 121.86, 123.71, 124.79, 124.83, 126.34, 126.65, 129.40, 129.61, 132.54, 132.68, 133.05, 133.13, 139.94, 150.38, 151.49, 158.67, 159.79 (Ar-C, C=N, C=O)
	570	58.81	4.12	19.81				
6m	542.11	57.55	3.53	20.65	1565 (C=C), 1625 (C=N), 1680 (C=O), 2900 (C-H al), 3035 (C-H ar), 3305 (N-H)	4.57 (s, 2H, SCH_2), 5.54 (s, 2H, CH_2CO), 7.20 (t, 1H, *J* = 4 Hz, Ar-H), 7.26-7.35 (m, 4H, Ar-H), 7.43-7.57 (m, 6H, Ar-H), 7.79 (d, 1H, *J* = 4 Hz, Ar-H), 7.99 (d, 1H, *J* = 4 Hz, Ar-H), 8.15 (s, 1H, CH-1,2,3-triazole), 12.84 (s, 1H, NH)	26.96 (SCH_2), 51.75 (NCH_2CO), 114.84, 114.91, 115.88, 115.97, 121.87, 123.88, 124.79, 124.80, 126.34, 126.87, 129.65, 129.87, 132.14, 132.88, 132.92, 133.13, 142.56, 150.76, 151.31, 158.57, 159.71 (Ar-C, C=N, C=O)
	542	57.77	3.62	20.86				
6n	556.13	58.26	3.80	20.13	1555 (C=C), 1625 (C=N), 1685 (C=O), 2915 (C-H al), 3045 (C-H ar), 3310 (N- H)	2.41 (s, 3H, CH_3), 4.57 (s, 2H, SCH_2), 5.52 (s, 2H, NCH_2CO), 7.21 (t, 1H, *J* = 4 Hz, Ar-H), 7.26-79 (m, 4H, Ar-H), 7.42-7.46 (m, 3H, Ar-H), 7.50-7.57 (m, 2H, Ar-H), 7.67 (d, 1H, *J* = 4 Hz, Ar-H), 7.77 (s, 1H, Ar-H), 8.15 (s, 1H, CH-1,2,3- triazole), 12.78 (s, 1H, NH)	21.00 (CH_3), 26.95 (SCH_2), 51.70 (NCH_2CO), 114.83, 114.90, 115.87, 115.96, 121.44, 124.78, 124.80, 125.63, 126.86, 129.64, 129.86, 132.13, 132.88, 132.92, 133.12, 133.43, 142.52, 150.82, 151.36, 158.56, 159.73 (Ar-C, C=N, C=O)
	556	58.07	3.89	20.32				
6o	620.09	52.25	3.41	18.05	1560 (C=C), 1610 (C=N), 1670 (C=O), 2940 (C-H al), 3060 (C-H ar), 3340 (N-H)	3.25 (s, 3H, CH_3), 4.57 (s, 2H, SCH_2), 5.56 (s, 2H, NCH_2CO), 7.20 (t, 1H, *J* = 4 Hz, Ar-H), 7.25-7.39 (m, 3H, Ar-H), 7.46-7.57 (m, 5H, Ar-H), 7.96-7.99 (m, 2H, Ar-H), 8.17 (s, 1H, CH-1,2,3-triazole), 8.66 (s, 1H, Ar-H), 12.89 (s, 1H, NH)	26.93 (SCH_2), 44.03 (CH_3), 51.87 (NCH_2CO), 114.84, 114.91, 115.87, 115.97, 121.06, 122.27, 124.81, 124.93, 125.61, 126.86, 129.66, 129.87, 132.12, 132.88, 132.91, 133.12, 133.61, 142.57, 150.85, 151.41, 158.56, 159.73 (Ar-C, C=N, C=O)
	620	52.42	3.32	17.86				

Table III. Antimicrobial screening of compounds ***4a-e*** *and* ***6a-o*** *expressed as* MIC

Compd.	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	Sp	*Bs*	*Sa*	*Pa*	*Ec*	*Kp*	*Af*	*Ca*
4a	16	31.25	31.25	31.25	16	31.25	31.25	31.25
	64.76	125.49	125.49	**125.49**	**64.76**	**125.49**	**125.49**	**125.49**
4b	16	31.25	31.25	31.25	16	31.25	31.25	31.25
	61.28	119.70	119.70	**119.70**	**61.28**	**119.70**	**119.70**	**119.70**
4c	16	16	31.25	16	16	31.25	31.25	16
	58.59	58.59	114.43	**58.59**	**58.59**	**114.43**	**114.43**	**58.59**
4d	16	31.25	31.25	31.25	16	16	31.25	31.25
	49.52	96.72	96.72	**96.72**	**49.52**	**49.52**	**96.72**	**96.72**
4e	16	16	31.25	16	16	31.25	31.25	16
	51.77	51.77	101.12	**51.77**	**51.77**	**101.12**	**101.12**	**51.77**
6a	16	16	16	16	8	8	16	16
	33.32	33.32	33.32	**33.32**	**16.66**	**16.66**	**33.32**	**33.32**
6b	8	8	16	16	16	8	16	8
	16.19	16.19	32.38	**32.38**	**32.38**	**16.63**	**32.38**	**16.19**
6c	8	8	16	16	8	16	8	8
	14.33	14.33	28.67	**28.67**	**14.33**	**28.67**	**14.33**	**14.33**
6d	16	16	16	16	8	16	16	8
	32.38	32.38	32.38	**32.38**	**16.19**	**32.38**	**32.38**	**16.19**
6e	8	16	16	16	16	8	16	8
	15.74	31.48	31.48	**31.48**	**31.48**	**15.74**	**31.48**	**15.74**
6f	8	8	16	16	8	16	8	8
	13.98	13.98	27.97	**27.97**	**13.98**	**27.97**	**13.98**	**13.98**
6g	4	8	16	16	8	16	8	8
	7.90	15.80	31.61	**31.61**	**15.80**	**31.61**	**15.80**	**15.80**
6h	8	8	16	16	8	8	8	4
	15.36	15.36	30.73	**30.73**	**15.36**	**15.36**	**15.36**	**7.68**
6i	4	8	8	8	8	4	4	4
	6.84	13.69	13.69	**13.69**	**13.69**	**6.84**	**6.84**	**6.84**
6j	8	16	16	16	16	16	16	8
	14.38	28.77	28.77	28.77	**28.77**	**28.77**	**28.77**	**14.38**
6k	8	16	16	16	16	8	16	8
	14.03	28.06	28.06	**28.06**	**28.06**	**14.03**	**28.06**	**14.03**
6l	8	8	16	16	8	8	8	8
	12.2	12.62	25.23	**25.23**	**12.62**	**12.62**	**12.62**	**12.62**

6m	4	8	8	8	8	8	8	4
	7.37	14.75	14.75	14.75	**14.75**	**14.75**	**14.75**	**7.37**
6n	4	8	8	8	8	4	8	4
	7.19	14.38	14.38	14.38	**14.38**	**7.19**	**14.38**	**7.19**
6o	4	4	8	8	4	4	4	4
	6.45	6.45	12.90	12.90	**6.45**	**6.45**	**6.45**	**6.45**
Cipro-floxacin	≤5	≤1	≤5	≤5	≤1	≤1	–	–
	≤15	≤3	≤15	**≤15**	**≤3**	**≤3**	–	–
Flucon-azole	–	–	–	–	–	–	≤1	≤1
	–	–	–	–	–	–	**≤3.26**	**≤3.26**

MIC – minimum inhibitory concentration (μg mL^{-1} or μmol L^{-1}, bold); *Af – Aspergillus fumigatus, Bs – Bacillus subtilis, Ca – Candida albicans, Ec – Escherichia coli, Kp – Klebsiella pneumoniae, Sa – Staphylococcus aureus, Sp – Streptococcus pneumoniae, Pa – Pseudomonas aeruginosa.*

RESULTS AND DISCUSSION

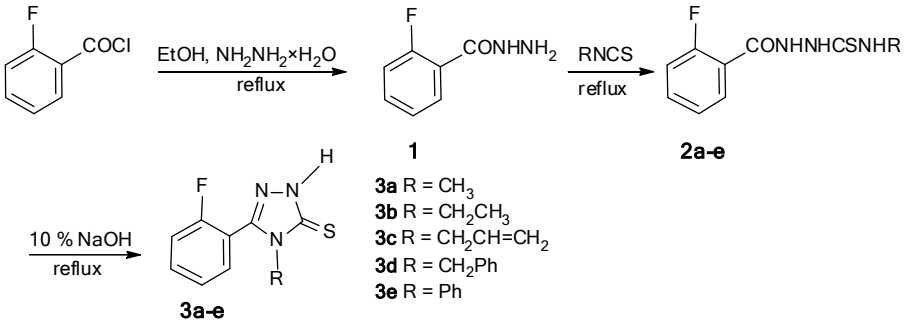
Chemistry

This study describes a regioselective synthesis of novel 1,4-disubstituted 1,2,3-triazoles based on benzothiazole-1,2,4-triazole conjugates through a stepwise reaction, as outlined in Schemes 1–3. Synthesis of the propargylated 1,2,4-triazole precursors required for the Cu(I)-catalyzed azide-alkyne cycloaddition reaction occurred first through the synthesis of fluorinated 1,2,4-triazole-3-thiones **3a**-**e**. Synthesis of the latter was accomplished according to the previously reported procedures with some modifications (26–28) (Scheme 1).

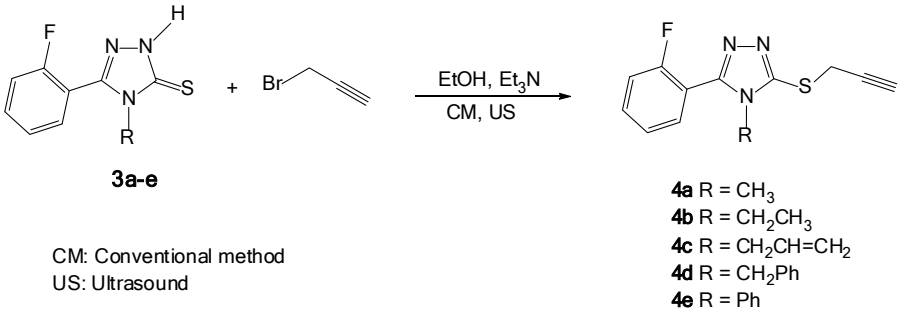
Commercially available 2-fluorobenzoyl chloride was subjected to esterification followed by hydrazidation to afford 2-fluorobenzohydrazide (1). The product was treated with diverse alkyl/aryl isothiocyanates to yield the corresponding acid thiosemicarbazide derivatives **2a**-**e**, which under optimized basic reaction conditions (10 % NaOH) underwent an oxidative ring closure to furnish the desired 1,2,4-triazoles **3a**-**e** (Scheme 1). It should be mentioned that the N^4-methyl and/or ethyl substituted triazoles **3a**,**b** were previously synthesized by nucleophilic addition of the appropriate substituted thiosemicarbazides to 2-fluorobenzoylchloride, followed by subsequent intramolecular cyclization of the resulting substituted acid thiosemicarbazides catalyzed by the suitable cyclodehydrating agent (26–28). In contrast, no references were available for the construction of the allyl and benzyl analogues **3c** and **3e**, respectively. In the presence of Et_3N as the basic catalyst, alkylation of the 1,2,4-triazole-3-thiones **3a**-**e** with propargyl bromide furnished the target thiopropargylated 1,2,4-triazole precursors **4a**-**e** required for the click synthesis. Their synthesis is displayed in Scheme 2.

The alkylation required heating for 1–2 h to afford the desired alkynes **4a-e** in 90–93 % yield while, under US irradiation, 15–20 min was required to give the product in 94–98 % yields (Table I).

The proton NMR spectral data of the propargylated-1,2,4-triazoles **4a-e** showed characteristic resonances at δ 2.24–2.29 ppm, which were assigned to the terminal hydrogen



Scheme 1.

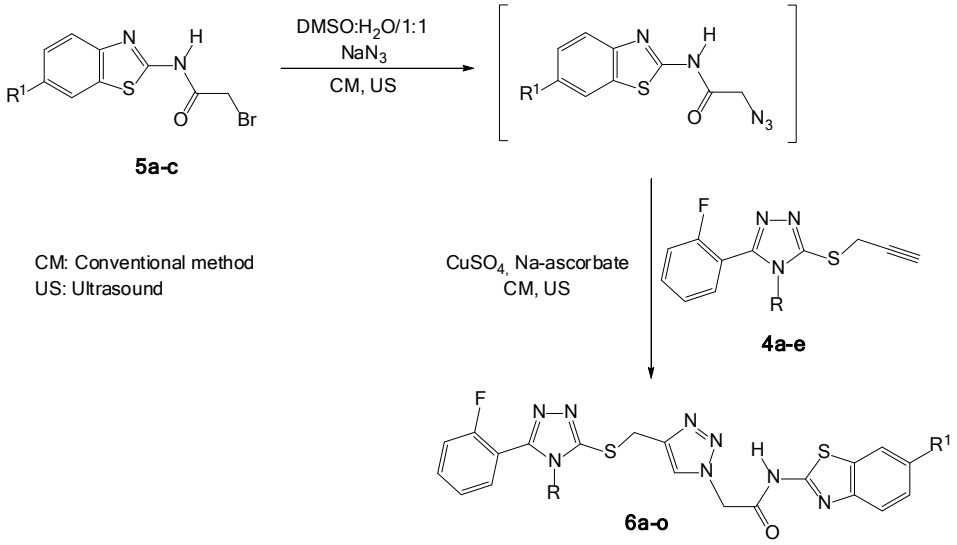


Scheme 2.

of the C≡C group. The thiomethylene protons resonated as a distinct singlet in the upfield region at δ 3.87–4.08 ppm. The ^{1}H NMR spectrum of compound **4a** also revealed the presence of a singlet at δ 3.51 ppm integrating for three protons assigned to the NCH_3 group of the 1,2,4-triazole ring. In the spectra of compounds **4d** and **4e**, five extra aromatic protons were observed in the aromatic region and assigned to the phenyl and/or benzyl rings bonded to the 1,2,4-triazole at position N-4. In the ^{13}C NMR spectra of compounds **4a-e**, the signals characteristic of the alkyne C≡C carbons resonated at δ 72.46–78.38 ppm, while the SCH_2 carbons appeared at δ 21.18–22.89 ppm. Additional signals were also observed in the aliphatic region for compounds **4a-d** attributed to the alkyl residue appended at the N-4 nitrogen of the 1,2,4-triazole ring.

The α-bromoacetamide benzothiazoles **5a-c** were synthesized based on our previously reported procedure (16) involving base-assisted acylation of the appropriate 2-aminobenzothiazoles with bromoacetyl bromide. The freshly prepared acetamide derivatives were subjected to an azidolysis reaction with sodium azide to give the azidoacetamide intermediates, which were coupled with the propargylated 1,2,4-triazoles **4a-e** under optimized Cu(I) catalyzed click synthesis to lead to the target novel 1,4-disubstituted 1,2,3-triazoles based on benzothiazole-1,2,4-triazole conjugates **6a-o** (Scheme 3).

Click synthesis was performed in the presence of $CuSO_4$ and Na-ascorbate as catalysts and DMSO-H_2O as the solvent, under both conventional thermal heating and ultrasound



6a R = CH_3, R^1 = H; **6b** R = CH_3, R^1 = CH_3; **6c** R = CH_3, R^1 = SO_2CH_3
6d R = CH_2CH_3, R^1 = H; **6e** R = CH_2CH_3, R^1 = CH_3; **6f** R = CH_2CH_3, R^1 = SO_2CH_3
6g R = $CH_2CH{=}CH_2$, R^1 = H; **6h** R = $CH_2CH{=}CH_2$, R^1 = CH_3; **6i** $CH_2CH{=}CH_2$, R^1 = SO_2CH_3
6j R = CH_2Ph, R^1 = H; **6k** R = CH_2Ph, R^1 = CH_3; **6l** R = CH_2Ph, R^1 = SO_2CH_3
6m R = Ph, R^1 = H; **6n** R = Ph, R^1 = CH_3; **6o** R = Ph, R^1 = SO_2CH_3

Scheme 3.

irradiation. As shown in Table II, the click synthesis performed under US irradiation was significantly accelerated; the reaction time decreased from 36–48 h to 6–8 h. In addition, yields of the click products were slightly higher (6–8 %) compared to those obtained with conventional thermal heating.

It was reported in the literature that the preparation of the 1,2,3-triazole ring was generally evidenced by the disappearance of the ≡C-H singlet and the appearance of a characteristic singlet in the aromatic region assignable to the 1,2,3-triazolyl proton (14, 15). Thus, in the ^{1}H NMR spectra of the 1,2,3-triazole conjugates **6a-o**, the presence of one distinct singlet at δ 8.06-8.17 ppm was attributed to the C-5H proton of the triazole ring and confirmed the success of the ligation of the azide residue of the benzothiazole moieties to the propargylated-1,2,4-triazole building blocks. The spectra also displayed two singlets at δ 4.50–4.60 and 5.51–5.61 ppm, which were assigned to the SCH_2 and CH_2CO protons, respectively. In addition, the amidic NH proton resonated as a broad singlet in the downfield region at δ 12.75–12.89 ppm. Formation of the 1,2,3-triazole scaffold was also supported by ^{13}C NMR analysis where the absence of the C≡C carbons was obvious in the spectra of compounds **6a-o**, which confirmed their formation in the click synthesis. The spectra also displayed additional resonances at δ 51.58–52.41 and 159.57–159.98 ppm, which were assigned, respectively, to the CH_2 and C=O carbons of the acetamide spacer incorporated between the benzothiazole and 1,2,3-triazole moieties. Elemental analyses of all compounds were within ± 0.4 % of the theoretical values.

Antimicrobiological activity and SAR

Using the broth dilution method (24, 25), the propargylated triazoles **4a-e** and their respective click products **6a-o** were assessed for their antibacterial and antifungal inhibition potencies. Results of the antimicrobial screening expressed in terms of *MIC* (Table III) revealed that most of the designed compounds displayed good to excellent antimicrobial activity against all of the tested strains with *MIC*s of 6.45–64.76 μmol L^{-1}. The antibacterial bioassay results for the propargylated triazole precursors **4a-e** revealed that all of the tested compounds exhibited moderate antibacterial inhibition activity towards all bacterial strains with *MIC* values of 49.52–125.49 μmol L^{-1}.

Incorporation of a 1,2,3-triazole based benzothiazole ring system in the structure of the 1,2,4-triazole ring enhanced markedly the antibacterial activity, as evidenced by the inhibition potency of the designed 1,2,3-triazole based benzothiazole-1,2,4-triazole conjugates **6a**-**o** with *MIC* values ranging from 6.45–33.32 μmol L^{-1}. The antibacterial profiles appeared to be dependent on the type of substitution at N-4 of the triazole ring, while the nature of substituents present on the benzothiazole ring did not play a vital role in the improvement of antibacterial activity.

It is evident from Table III that most of the designed 1,2,3-triazole conjugates **6** were effective against *S. pneumoniae* with *MIC* values of 6.45–33.32 μmol L^{-1}. Compounds **6g-o** were found to exhibit comparable and/or higher antibacterial activity compared to the standard drug ciprofloxacin. Notably, 1,2,3-triazoles **6m-o** resulting from the optimum combination of the 4-phenyl-1,2,4-triazole ring and un/substituted benzothiazole ring exerted the highest antimicrobial activity in general: the best anti-*S. pneumoniae* activity with *MIC* values of 6.45–7.37 μmol L^{-1} and activity against *S. aureus* and *P. aeruginosa* with *MIC* values of 12.90–14.75 μmol L^{-1} in all cases being more potent than the standard drug ciprofloxacin.

The antifungal bioassay results showed that most of the tested 1,2,3-triazole conjugates **6a-o** were effective against *A. fumigatus* and *C. albicans* with *MIC* values of 6.45–33.32 μmol L^{-1}. Among them, compound **6o** with phenyl substitution at the 4th position of the 1,2,4-triazole ring and methylsulfonyl group at the 6th position of the benzothiazole ring exhibited the highest antifungal inhibition potency towards *A. fumigatus* and *C. albicans* with *MIC* values of 6.45 μmol L^{-1}. Compounds **6g-i** and **6j-l** with allyl and benzyl substitution at the 4th position also displayed significant potency against the two fungal strains with *MIC* values of 6.84–15.80 μmol L^{-1} (**6g-i**) and 12.62–28.77 μmol L^{-1} (**6j-l**), respectively.

The antimicrobial behavior of the benzothiazole-based 1,2,3-triazoles followed the same trend as their analogues described in our other published work (16). In contrast, the moderate antifungal activity reported previously increased significantly in the present work. Presumably, this could be due to the presence of the 1,2,4-triazole moiety, which conferred antifungal activity. These results are in agreement with the literature, where the excellent antifungal activity exhibited by several commercial antifungal drugs, including fluconazole, itraconazole, voriconazole and posaconazole, was attributed to the incorporation of the 1,2,4-triazole core in their structures (29, 30).

CONCLUSIONS

In summary, new compounds, propargylated 1,2,4-triazoles **4a**-**e** and their corresponding 1,2,3-triazoles **6a**-**o** were synthesized and fully characterized. We designed and

synthesized a novel series of 1,2,3-triazole-1,2,4-triazole molecular conjugates linked to a bioactive benzothiazole scaffold *via* an acetamide spacer utilizing the Cu(I)-catalyzed multicomponent click chemistry approach under both conventional and ultrasound conditions. The newly designed *N*-(un/substituted benzo[*d*]thiazol-2-yl)-4-alkyl/aryl-2-(4-(((5-(2-fluorophenyl)-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)-acetamides **6a-o** were assessed for their antimicrobial activity against a panel of pathogenic bacterial and fungal strains. Antimicrobial studies showed that most of these conjugates exhibited good to excellent activity against all of the tested strains. These results revealed a significant dependence of the antimicrobial inhibition activity on N-4 substitution on the 1,2,4-triazole ring as well as the nature of substitution at C-6 of the benzothiazole ring with marked preference of SO_2CH_3 substitution over H and CH_3.

REFERENCES

1. S. Pancholia, T. M. Dhameliya, P. Shah, P. S. Jadhavar, J. P. Sridevi, P. Yogeshwari, D. Sriram and A. K. Chakraborti, Benzo[*d*]thiazol-2-yl(piperazin-1-yl)methanones as new anti-mycobacterial chemotypes: Design, synthesis, biological evaluation and 3D-QSAR studies, *Eur. J. Med. Chem.* **116** (2016) 187–199; DOI: 10.1016/j.ejmech.2016.03.06
2. P. Shah, T. M. Dhameliya, R. Bansal, M. Nautiyal, D. N. Kommi, P. S. Jadhavar, J. P. Sridevi, P. Yogeeswari, D. Sriram and A. K. Chakraborti, *N*-arylalkylbenzo[*d*]thiazole-2-carboxamides as antimycobacterial agents: design, new methods of synthesis and biological evaluation, *Med. Chem. Commun.* **5** (2014) 1489–1495; DOI: 10.1039/C4MD00224E.
3. X. Chai, J. Zhang, S. Yu, H. Hu, Y. Zou, Q. Zhao, Z. Dan, D. Zhang and Q. Wu, Design, synthesis, and biological evaluation of novel 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4- difluorophenyl)-3-substituted benzylamino-2-propanols, *Bioorg. Med. Chem. Lett.* **19** (2009) 1811–1814; DOI: 10.1016/j.bmcl.2009.01.048.
4. M. H. Miceli and C. A. Kauffman, Isavuconazole: a new broad-spectrum triazole antifungal agents, *Clin. Infect. Dis.* **61** (2015) 1558–1565; DOI: 10.1093/cid/civ571.
5. Y. Uygun, H. Bayrak and H. Özkan, Synthesis and biological activities of methylenebis-4*H*-1,2,4-triazole derivatives, *Turk. J. Chem.* **37** (2013) 812–823; DOI: 10.3906/kim-1212-66.
6. W. Yanwei, X. Kehan, B. Guojing, H. Lei, W. Qiuye, P. Weihua and Y. Shichong, Synthesis and antifungal activity of novel triazole compounds containing piperazine moiety, *Molecules* **19** (2014) 11333–11340; DOI: 10.3390/molecules190811333.
7. R. P. Sambasiva, C. Kurumurthy, B. Veeraswamy, K. G. Santhosh, Y. Poornachandra, K. C. Ganesh, S. B. Vasamsetti, S. Kotamraju and B. Narsaiah, Synthesis of novel 1,2,3-triazole substituted-*N*-alkyl/aryl nitrone derivatives, their anti-inflammatory and anticancer activity, *Eur. J. Med. Chem.* **80** (2014) 184–191; DOI: 10.1016/j.ejmech.2014.04.052.
8. H. S. Mubarak, D. S. Dnyaneshwar, N. Laxman, S. Dhiman, http://pubs.rsc.org/en/results?searchtext=Author%3ADhiman%20SarkarA. K. K. Firoz, N. S. Jaiprakash and B. S. Bapurao, 1,2,3-Triazole derivatives as antitubercular agents: synthesis, biological evaluation and molecular docking study, *Med. Chem. Commun.* **6** (2015) 1104–1116; DOI: 10.1039/C5MD00057B.
9. S.-Y. Zhang, D.-J. Fu, X.-X. Yue, Y.-Ch. Liu, J. Song, H.-H. Sun, H.-M. Liu and Y.-B. Zhang, Design, synthesis and structure-activity relationships of novel chalcone-1,2,3-triazole-azole derivatives as antiproliferative agents, *Molecules* **21** (2016) 653–665; DOI: 10.3390/molecules21050665.
10. L.-Y. Ma, L.-P. Pang, B. Wang, M. Zhang, B. Hu, D.-Q. Xue, K.-P. Shao, B.-L. Zhang, Y. Liu, E. Zhang and H.-M. Liu, Design and synthesis of novel 1,2,3-triazole-pyrimidine hybrids as potential anticancer agents, *Eur. J. Med. Chem.* **86** (2014) 368–380; DOI: 10.1016/j.ejmech.2014.08.010.

11. N. R. Penthala, L. Madhukuri, S. Thakkar, N. R. Madadi, G. Lamture, R. L. Eoff and P. A. Crooks, Synthesis and anti-cancer screening of novel heterocyclic-(2*H*)-1,2,3- triazoles as potential anti-cancer agents, *Med. Chem. Commun*. **6** (2015) 1535–1543; DOI: 10.1039/C5MD00219B.
12. K. T. Petrova, T. M. Potewar, P. Correia-da-Silva, M. T. Barros, R. C. Calhelha, A. Ćiric, M. Soković and C. F. R. Ferreira, Antimicrobial and cytotoxic activities of 1,2,3-triazole-sucrose derivatives, *Carb. Res*. **417** (2015) 66–71; DOI: 10.1016/j.carres.2015.09.003.
13. N. Li, D. Wang, J. Li, W. Shi, Ch. Li and B. Chen, One-pot synthesis of 4,5-disubstituted 1,2,3-(NH)-triazoles using terminal acetylenes, carbon monoxide, aryl iodides, and sodium azide, *Tetrahedron Lett*. **52** (2011) 980–982; DOI: 10.1016/j.tetlet.2010.12.053.
14. J. T. Fletcher and J. E. Reilly, Fast dye salts provide fast access to azidoarene synthons in multi-step one-pot tandem click transformations, *Tetrahedron Lett*. **52** (2011) 5512–5515; DOI: 10.1016/j.tetlet.2011.08.069.
15. K. Barral, A. D. Moorhouse and J. E. Moses, Efficient conversion of aromatic amines into azides: a one-pot synthesis of triazole linkages, *Org. Lett*. **9** (2007) 1809–1811; DOI: 10.1021/ol070527h.
16. G. Zbancioc, I. I. Mangalagiu and C. Moldoveanu, Ultrasound assisted synthesis of imidazolium salts: an efficient way to ionic liquids, *Ultrason. Sonochem*. **23** (2015) 376–384; DOI: 10.1016/j.ultsonch.2014.10.028.
17. G. Ameta, P. A. Kumar, C. Ameta, R. Ameta and P. B. Punjabi, Sonochemical synthesis and characterization of imidazolium based ionic liquids: A green pathway, *J. Mol. Liq*. **211** (2015) 934–937; DOI: 10.1016/j.molliq.2015.08.009.
18. N. Rezki, A green ultrasound synthesis, characterization and antibacterial evaluation of 1,4-disubstituted 1,2,3-triazoles tethering bioactive benzothiazole nucleus, *Molecules* **21** (2016) 505–516; DOI: 10.3390/molecules21040505.
19. M. R. Aouad, M. Messali, N. Rezki, A. A. Ali and A. Lesimple, Synthesis and characterization of some novel 1,2,4-triazoles, 1,3,4-thiadiazoles and Schiff bases incorporating imidazole moiety as potential antimicrobial agents, *Acta Pharm*. **65** (2015) 117–132; DOI: 10.1515/acph-2015-0011.
20. N. Rezki, A. M. Al-Yahyawi, S. K. Bardaweel, F. F. Al-Blewi and M. R. Aouad, Synthesis of novel 2,5-disubstituted-1,3,4-thiadiazoles clubbed 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole and/or Schiff base as potential antimicrobial and antiproliferative agents, *Molecules* **20** (2015) 16048–16067; DOI: 10.3390/molecules200916048.
21. D. Kumar, D. N. Kommi, N. Bollineni, A. R. Patel and A. K. Chakraborti, Catalytic procedures for multicomponent synthesis of imidazoles: selectivity control during the competitive formation of tri- and tetrasubstituted imidazoles, *Green Chem*. **14** (2012) 2038–2049; DOI: 10.1039/C2GC35277J.
22. D. Kumar, M. Sonawane, B. Pujala, V. K. Jain, S. Bhagat and A. K. Chakraborti, Supported protic acid-catalyzed synthesis of 2,3-disubstituted thiazolidin-4-ones: enhancement of the catalytic potential of protic acid by adsorption on solid supports, *Green Chem*. **15** (2013) 2872–2884; DOI: 10.1039/C3GC41218K.
23. S. R. Roy, P. S. Jadhavar, K. Seth, K. K. Sharma and A. K. Chakraborti, Organocatalytic application of ionic liquids: [bmim][$MeSO_4$] as a recyclable organocatalyst in the multicomponent reaction for the preparation of dihydropyrimidinones and -thiones, *Synthesis* **14** (2011) 2261–2267; DOI: 10.1055/s-0030-1260067.
24. European Committee for Antimicrobial Susceptibility Testing (EUCAST), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution, *Clin. Microb. Infect*. **6** (2000) 509–515; DOI: 10.1046/j.1469-0691.2000.00142.x.
25. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Approved Standard M7-A5, 5th ed., NCCLS, Wayne (PA) 2000.

26. J. M. Kane, M. W. Dudley, S. M. Sorensen and F. P. Miller, 2,4-Dihydro-3*H*-1,2,4-triazole-3-thiones as potential antidepressant agents, *J. Med. Chem.* **31** (1988) 1253–1258; DOI: 10.1021/jm00401a031.
27. J. M. Kane, C. R. Dalton, M. A. Staeger and E. W. Huber, Long-range fluorine-proton coupling in 1,2,4-triazole derivatives, *J. Heterocyclic Chem.* **32** (1995) 183–187; DOI: 10.1002/jhet.5570320130.
28. T. Jianying, S. Yanxia, L. Xinghai, S. Nabo and L. Baoju, Synthesis and fungicidal activity of 1,2,4-triazole derivatives containing 2-fluorophenyl moiety, *Chin. J. Org. Chem.* **32** (2012) 2373–2377; DOI: 10.6023/cjoc201207020.
29. A. H. Groll and J. Lumb, New developments in invasive fungal disease, *Future Microbiol.* **7** (2012) 179–184; DOI: 10.2217/fmb.11.154.
30. A. Kleeman, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances*, 3rd ed., Thieme, Stuttgart-New York 1999, pp. 2286.